A new frame of mind

Drs Naoki Masuda and Takamitsu Watanabe discuss their innovative method for estimating the activity of resting-state brain networks that has proved to be more accurate than currently popular techniques.

How did you come to develop an interest in computational neuroscience?

NM: During my PhD, I worked on the coding theory of information processing in the brain, using computational models of neuronal networks. My interests gradually drifted from coding theory to more concrete topics in computational neuroscience, in particular networks and social behaviour/dynamics, and studying functional magnetic resonance imaging (fMRI) data and the networks elicited by them.

TW: Although conventional methods of analysing fMRI data have actually provided lots of astonishing insights about brain functions, they did not seem to be the most appropriate way to tackle dynamics of cognitive functions. I began to search for other paradigms to investigate the theme; computational neuroscience among them.

Why is increasing understanding of resting-state brain networks (RSNs) so important?

TW: An RSN is supposed to consist of important brain regions that mainly support functions such as reprocessing of memory into more access-friendly forms and self-referential thinking, which is essential for a person’s sense of identity. Therefore, nowadays we think that better understanding of RSNs will tell us why resting is necessary for our brain and how often we should do this. Ultimately, such information might be a great help for preventing and treating some mental illnesses such as depression, and may also be useful as a basis for tools to enhance human potential.

NM: RSNs also tell us many things about non-resting brain activity, memory function, cognitive processes, etc. We focus on a particular set of regions of interest and examine dynamics and correlated activity.

Could you provide an insight into the background behind this study? How has it fit the model of networks consisting of more than 10 brain regions requires a fairly large amount of resting-state fMRI data. Fortunately, we obtained this from our colleagues, who went to considerable efforts in building a dataset of resting-state fMRI signals. We hope to continue to collaborate in this way in the future.

Where do you intend to focus future efforts?

NM: An obvious application is to apply the model to other types of brain networks. For now, MEM is suitable for estimating small networks, but we are working on applying the model to large-scale brain networks. We can also infer changes in the strength of functional interactions by using this method. In a forthcoming study based on the same model, we aim to demonstrate such dynamics during sleep. This information will help to elucidate the role of sleep and different functions of those stages through the natural cycle.

TW: In addition, we are now trying to apply this method to fMRI signals that were obtained during certain psychological tasks. We hope that this new application will reveal neural mechanisms that induce cognitive dynamics.

TW: Many previous RSN and similar functional brain network studies were dependent on simple brain activity correlations among brain regions. So-called functional connectivity is actually a very useful index to assess the functional interactions in brain networks, but it is also the case that some pairs of brain regions without direct anatomical connections show large values of functional connectivity. Our recent study also showed that a region pair can exhibit a strong correlation between them if another brain region has anatomical connections with both of these regions. How to exclude such pseudofunctional interactions has been one of the major problems behind conventional correlation-based functional connectivity. Our work reveals how to minimise detection of such pseudofunctional connectivity.

Had maximum entropy models (MEMs) been used for the estimation of neural activity prior to your investigation?

NM: MEMs have been used in various fields (outside neuroscience) under different names since the 1950s, such as the Boltzmann machine, Ising model, log-linear model in statistical physics and statistical sciences, and also in other biological domains. In neuroscience, the first use of MEMs appeared in 2006 by Dr Elad Schneidman and collaborators in an article in Nature. They applied MEMs to electrophysiological data and found a relatively simple variant of the MEM – the so-called pairwise MEM – is sufficient to capture most of the information contained in spike trains emitted from presumably interconnected (perhaps indirectly) neurons. Within neuroscience, all studies focused on action potentials of neurons or local field potentials, as far as we know. So we considered the possibility of applying this method to fMRI data.

Have you faced any particular challenges over the course of your work?

TW: One of the greatest challenges in this study was collecting fMRI data. To analy
Current methods for analysing functional magnetic resonance imaging data from the resting brain have proved inadequate for some purposes, but a team from the University of Tokyo in Japan has found a promising alternative.

During rest, the human brain remains active, engaging in a number of fundamental and intrinsic functions such as self-referential cognitive processes, maintenance of memory and attentional cognitive processes. Researchers have investigated this state using positron emission tomography or functional magnetic resonance imaging (fMRI), uncovering that a large amount of spontaneously fluctuating activity recorded during rest is highly correlated between multiple interacting brain regions.

The complex interactions between regions of the brain thought to support these resting functions are called resting-state networks (RSNs), and a better understanding of RSNs will provide rich information about resting and why it is necessary. This knowledge may ultimately aid the treatment of various mental illnesses and provide the basis for methods of boosting potential cognitive ability. However, neuroscientists have yet to quantify the level of complexity observed in the activities of a collection of brain regions and in the overall structure of these functional interactions in RSNs. Without this information, it is difficult to comprehensively understand this brain activity as an integrative large-scale neural system.

Data Analysis

There are currently several methods of analysing fMRI data during rest, but finding correlations between signals at two locations in the brain is the most common and intuitive way to estimate the presence and strength of connectivity between two RSN regions. At present, by far the most widely used method of estimating the complexity of functional interactions in the resting brain is functional connectivity (FC) analysis, which is based on Pearson’s correlation coefficient between a pair of brain regions.

However, the FC-based method seriously suffers from pseudocorrelation, when pairs of brain regions that are not directly connected appear to exhibit functional connectivity. For example, if brain regions A and B are adjacent to each other, and so are B and C, but A and C are only connected through B and not linked directly, a conventional correlation-based method would find a correlation between A and C as well as the adjacent regions. Furthermore, one particular study employing monkeys has shown that a pair of brain regions that does not have a direct anatomical connection may still exhibit a large FC value if the regions receive common input from a third region. Other studies also reveal that a significant FC reading between a pair of brain regions does not distinguish a monosynaptic (direct) connection from a polysynaptic (indirect) one.

Potentially rich information such as this may be discarded using FC-based methods, but would be revealed if the fact that functional interactions influence each other were taken into account. One of the major problems with this conventional FC method has been finding an effective way to exclude pseudocorrelations and retain potentially important information.

Decreasing Pseudocorrelations

With this in mind, Drs Naoki Masuda and Takamitsu Watanabe, and their team from the University of Tokyo, Japan, began exploring other methods that decreased the detection of pseudocorrelations. Watanabe felt that current methods of data analysis in experimental neuroscience were inadequate. With Masuda’s theoretical background in computational neuroscience they were able to develop new paradigms with which to handle fMRI data. They decided to test the possibility of using maximum entropy models (MEMs), which had been used before in estimating the complexity of activity patterns in microscopic neural tissues. This study was the first to apply MEMs to fMRI signals.
The pairwise MEM does not estimate functional interactions as a simple collection of pairwise interactions that are determined independently of each other, unlike those estimated by the FC-based technique. Instead, the MEM uses global activity patterns – activities of more than two sites that are considered simultaneously – to infer the organisation of functional interactions. A method based on a pairwise MEM would not include the assumption that activity patterns of region pairs are independent of those of other pairs. Therefore, if the pairwise MEM can accurately describe RSNs, it is expected to be better at assessing integrative network structure than the FC-based method.

**AN UNLIKELY CANDIDATE**

Until it was tested, the MEM seemed unlikely to produce adequate results because it requires the activity state of the estimated network to be binarised – a procedure that classifies continuous fMRI signals into two categories consisting of 1 and 0. In their study, Masuda and Watanabe’s team labelled fMRI signals above a particular threshold as 1 and weaker signals as 0. Doing so loses rich information and was expected to prevent an accurate fit between simulation and data. However, when applied this method produced a surprisingly accurate and robust result.

Although the researchers are yet to explore the detailed reasons as to why binarisation did not impair the accuracy of their fit, they speculate it may be because fMRI signals represent changes in blood oxygen level induced by neuronal activity, originally based on a binary train of spike data.

**A GOOD FIT**

These findings suggest that large-scale human brain networks during rest can be accurately captured by a relatively simple binary model. Masuda and Watanabe’s team has since tested their MEM against other newly developed or newly applied methods, including the mutual information (MI) method, inverse Gaussian model and partial correlation method. All of these techniques promised to be more robust against pseudocorrelations than FC, but the pairwise MEM method has vastly outperformed them all. Although the reasons are unclear, the team has demonstrated that the functional connections of human RSNs estimated by the MEM reflect anatomical connections with an unsurpassed accuracy.

**APPLICATIONS BEYOND RSNs**

Now that this technique has achieved some success in the pursuit of enhanced understanding of human RSNs, Masuda and Watanabe are exploring the potential applications of their MEM in other areas and fields, and are working on applying the method in novel ways. The logical next step would be to apply the technique to fMRI data from other brain networks. Until now, it has only been applied to small-scale networks such as RSNs, but the team’s findings indicate that their relatively simple statistical model provides a possible route to deriving physiological information about various large-scale brain networks.

A new study by the investigators, applying their model to fMRI data during sleep, is currently being reviewed in a neuroscience journal. Using the MEM’s ability to infer the strength of functional interactions in the brain, the researchers have collected information on the role of sleep and how the network structure changes in different phases of sleep.

The same methodology can also be applied to different types of data, such as fMRI data obtained during cognitive tasks, revealing neural mechanisms that induce cognitive dynamics. Masuda and Watanabe plan to continue their investigations by collaborating with others to accumulate data on which to apply their innovative model, in the hope of unlocking important messages hidden within.

**FURTHER READING**